DETAILED ACTION

1. Applicant's remarks and 1.132 declaration of Inventor Zaghouani filed 5/20/11 are acknowledged.

2. Claims 8-12, 20, 21, and 25 stand withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to non-elected inventions.

Claims 1-5, 7, 13, 15-19, 22-24, and 26-30 are under examination.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-5, 7, 13, 15-19, 22-24, and 26-30 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Specifically, the specification provides insufficient evidence that the claimed method could effectively function as a method for preventing or delaying the onset of type I diabetes (IDDM) in humans.

As set forth previously, While the mechanism of action for the method of the instant claims is not disclosed, it appears to require inducing tolerance to a GAD peptide. Tolerance-inducing peptide immunotherapy is well known in the immunological arts. In some cases significant results have been demonstrated in in-bred small animal models. However, said results have not been repeated in human trials. See for example, *Marketletter* (9/13/99) which teaches the complete failure in human trials of two peptides designed for tolerance induction. Both Myloral (for multiple sclerosis, MS) and Colloral (for rheumatoid arthritis, RA) provided successful results in rodent models (EAE and collagen induced arthritis, respectively). See also Leslie (2010) paraphrasing an interview with Dr. Mark Davis wherein Dr. Davis states that in the case of the administration of MBP for tolerance induction to MBP for the treatment of MS, while the method worked in mice, it actually made MS worse in some humans.

More specifically regarding the treatment of diabetes, see Pozzilli et al. (2000) wherein the authors demonstrate that, while the induction of tolerance to orally administered insulin for the treatment of diabetes might have been expected, it simply did not occur. The authors could only speculate as to the

reasons for the trial's failure. The authors did note one complicating factor that has been reported several times, and will have to be considered in all future work, a large placebo effect wherein both the treated and control subjects showed similar temporary improvement. Three years later Skyler et al. (2005) reported another failure in one of the largest placebo-controlled tolerance trials ever performed in humans (the administration of insulin for the prevention of type 1 diabetes).

As set forth above, the references demonstrate that peptides that work to induce immune tolerance in *in vivo* small animal disease models cannot be routinely expected to work in humans, i.e., they are unpredictable and requiring of undue experimentation.

Other investigators have discussed additional problems in establishing human tolerance. See, for example, Dong et al. (1999):

> "Despite the fact that it has been relatively easy to induce true tolerance in small experimental animals, translating these studies into larger animals and humans has been much more difficult to achieve. Some of the hurdles that may explain this dilemma are summarized in Table 3. *Even if we have the ideal strategy to use in humans, the lack of reliable predictable assays for rejection or tolerance still does not allow us to know if a patient is truly tolerant so that immunosuppressive agents may be withdrawn*",

emphasis added.

WO 02/053092 teaches that the oral administration of antigens (a route of administration encompassed by the claimed method) for the induction of tolerance presents numerous additional "obstacles", including the problem of accurate dosing given the necessity of digestion which alters both concentration and structure of the antigens. In that work the inventors conclude that:

> "oral and mucosal tolerance cannot be deduced from antigenic activity in conventional immunization, or even *in vitro* results, and must result from extensive empirical experimentation,"

In another attempt to explain these repeated failures Goodnow (2001) states:

> "Obtaining the desired response [tolerance] with these strategies [tolerance induction] is unpredictable because many of these signals [tolerogenic] have both tolerogenic and immunogenic roles,"

(see the Abstract). The author goes on to teach that while the induction of oral tolerance might be considered "an attractive notion", the method has failed in humans because of the lack of understanding of the mechanisms involved (page 2120, column 2).

More recently, Kraus and Mayer (2005) looked at tolerance induction in inflammatory bowel disease (IBD). They reported the ease with which tolerance is induced in in-bred experimental mice and contrasted that with the difficulty in inducing tolerance in humans. Speculating on the reasons for the difference the authors considered a lack of dosing optimization but went on to report that *the mechanisms of tolerance induction in humans and mice appear to be fundamentally different*. Most importantly, Kraus and Mayer report a genetic component wherein many IBD patients and their family members appear to be *incapable* of becoming

tolerant to oral antigens because they lack the ability to generate the required T regulatory cells. If confirmed, this would mean that *no* tolerance induction regime could work in these patients.

Even more recent work has attempted to duplicate favorable results established in in-bred animal models in a more complex mouse model more realistic to the out-bred human population. See, for example, Bell et al. (2008). The authors employed F_1 hybrid mice (a cross between two in-bred strains) wherein they asked if toleragens that worked in the parent strains would induce tolerance in the crossed F_1 hybrid mice. Unfortunately the results showed that in one instance not only was tolerance not induced, but disease was actually exacerbated. Thus, the work serves as a clear demonstration that the induction of immune tolerance is far from predictable in anything other than carefully chosen in-bred experimental mouse strains.

Also note that Applicant has referred to the NOD mouse as the "gold standard" for diabetes research. Others, however, refer to the NOD mouse as the "workhorse" for diabetes research pointing out the model's limitations. See, for example von Herrath and Nepom (2009). And note that not even all NOD mouse strains are diabetes susceptible, e.g., NOD H-2^k and NOD DQ8 do not develop the disease. Also note that it is well-known that tolerance to GAD is **not** effective for the treatment of diabetes in another well-established diabetes model, the BB rat. Even more recently many scientists have begun to question the value of mouse data altogether. As pointed out by Mark Davis in a recent interview, mice make a "lousy model" for the human immune system. He refers to mice as a short-lived rodent who's immune system has adapted for scurrying around with its nose in the dirt (Leslie, 2010). Also very recently van der Worp et al. (2010) question the value of using animal data to predict the effectiveness of treatment strategies in human trials. As an example, the authors teach that of about 500 effective treatment strategies for stroke in experimental mice, just 2 have proven effective in humans. The authors cite numerous possible reasons for the failed translation of results, including insufficient statistical power, inadequate animal data, overoptimistic conclusions, flawed studies, and the use of animal models that do not reflect real disease in humans. Finally the reference teaches that neutral and negative animal studies may remain unpublished leading to possibly false impressions of efficacy.

A review of the instant specification shows just a single long example wherein a T cell response to a single insulin B chain peptide (amino acids 9-23) is inhibited in the experimental NOD mouse model of IDDM. First note that the instant claims are drawn to the use of GAD, not insulin, for the suspending, preventing or delaying the onset of IDDM. Thus, the specification offers *no* data in support of the claimed method. Interestingly, the specification discloses, that even regarding the use of an insulin peptide for the suspending, preventing or delaying the onset of IDDM, *the method of the instant claims cannot function as claimed*, (emphasis added). For example, at page 28 of the specification, it is disclosed that, "Soluble Ig-INSβ displayed dose dependent delay of diabetes when given at either stage [pre or post IAA conversion]. However, aggregated Ig-INSβ, which induced IL-10 and TGFβ-producing T cells, thus involving sustained endogenous IL-10, was protective against diabetes when given before development of insulitis *but had no effect in predisposed mice positive for IAA*", emphasis added. Further, Examples 7 and 9 teach that neither soluble nor aggregated Ig-INSβ can actually prevent IDDM, but rather can only delay onset under specific conditions.

Additionally, Applicant's subsequent work demonstrates that the method of the instant claims would not be expected to function as claimed. See for example Legge et al. (1998). Therein the authors teach that APLs function as, "T cell

antagonists, partial agonists, or super agonists" (page 106). The authors go on to teach that PLP-LR stimulated PLP-1 specific T cells (paragraph spanning page 109 and 110), i.e., the T cells that would be pathogenic in an MS patient. Given that *no* experiments have been performed employing GAD peptides and derivatives thereof, it is just as likely that the method of the instant claims would actually exacerbate disease as treat or prevent it.

A set forth in *Rasmusson v. SmithKline Beecham Corp.*, 75 USPQ2d 1297, 1302 (CAFC 2005), enablement cannot be established unless one skilled in the art "would accept without question" an Applicant's statements regarding an invention, particularly in the absence of evidence regarding the effect of a claimed invention. Specifically:

> "As we have explained, we have required a greater measure of proof, and for good reason. If mere plausibility were the test for enablement under section 112, applicants could obtain patent rights to "inventions" consisting of little more than respectable guesses as to the likelihood of their success. When one of the guesses later proved true, the "inventor" would be rewarded the spoils instead of the party who demonstrated that the method actually worked. That scenario is not consistent with the statutory requirement that the inventor enable an invention rather than merely proposing an unproved hypothesis."

Thus, in view of the quantity of experimentation necessary, the lack of sufficient guidance in the specification, the lack of sufficient working examples, i.e., the specification discloses **no** data regarding the treatment or prevention of IDDM employing GAD peptides, and the unpredictability of the art, it would take undue trials and errors to practice the claimed invention.

Applicant's arguments, filed 5/20/11, have been fully considered but are not found persuasive. Applicant alleges, "the PTO has not provided any credible evidence showing that one of ordinary skill in the art would ***reasonably doubt*** the asserted utility of the claimed invention and has therefore not met its initial burden" (emphasis by Applicant).

Applicant is advised that no rejection for lack of utility has been made. The invention would most certainly have utility if it functioned as claimed in humans. Type 1 diabetes is a growing scourge on the human population; its prevention would most certainly be one of the greatest achievements in medical history.

Applicant alleges, "the sum total the evidence provided by the Patent Office shows that, using fundamentally different therapeutic agents than presently claimed, tested in diseases other than Type 1 diabetes as presently claimed, some researchers have achieved tolerance results in animal models that have been difficult to reproduce in humans."

Applicant's position is at best, overstated. If the therapeutic agents of the cited references are actually "fundamentally different", then Applicant's method of preventing or delaying type 1 diabetes would likely function through a "fundamentally different" mechanism unknown to biological science. As such, said mechanism would require significant enablement comprising, at the very least, some sort of sound scientific reasoning as to why the ordinarily skilled artisan would have any expectation of success employing Applicant's revolutionary method in the treatment of human disease. Further, it is unclear how Applicant can credibly allege that the diseases of the cited references are "diseases other than Type 1 diabetes" when at least Pozzilli et al. and Skyler et al. specifically report failures in attempted treatments of type 1 diabetes. Applicant is advised that mischaracterizing facts of record does not comprise a persuasive argument.

Citing MPEP 2164.05(a), Applicant again argues that post-filing date references cannot be used in an enablement rejection. Applicant cites *In re Wright* (cited in MPEP 2164.05(a)) and opines on the holdings of the court.

Interestingly, what Applicant fails to point out is that, similar to fact pattern in the instant application, the examiner in the Wright application cited a post-filing reference (Matthews et al.) showing that even some years post-filing the treatment was ineffective in preventing disease in animal models, that animal models were "likely to be imperfect", and that testing in humans was "necessary to determine safety, immunogenicity, and efficacy." The court itself further found relevant the fact that even years after the Wright invention no one had yet developed a "generally successful AIDS virus vaccine". The court also found relevant the fact that the Examiner noted that the scientific community was having difficulty developing an AIDS vaccine years after the filing of the Wright application, "to illustrate that the art is not even today [10 years later] as predictable as Wright has suggested that it was back in 1983." This fact is particularly relevant to the method of the instant claims wherein some 9+ years after the priority date of the instant application no antigen-specific treatments, much less preventions, for type 1 diabetes are known. More specifically, antigen-specific treatments have been tried in humans and failed, see Pozzilli et al. and Skyler et al.

Applicant dismisses the teachings of the Marketletter, Pozzilli et al., Dong et al., Legge et al, and Goodnow.

Applicant's dismissal is noted. The references still serve, however, to teach the unpredictability of establishing immune tolerance in humans. And again, if Applicant's method does not function through the establishment of immune tolerance, then said method would be truly revolutionary in the biological sciences and requiring of more enablement than is set forth in the instant specification which includes no showing of the delaying or preventing of type 1 diabetes employing the GAD construct of the instant claims.

Applicant cites the Inventor's previously submitted 1.132 declaration as showing that the IgGAD2 construct of the instant claims could delay hyperglycemia in the NOD experimental mouse model. Applicant further refers to the NOD mouse model as the "gold standard animal model".

Applicant's position seems to be that while post-filing demonstrations of a lack of enablement are impermissible, post-filing demonstrations of enablement are permissible. Said position would seem to be contradictory. Turning again to *In re Wright*, the court dismissed the post-filing submissions of the Inventor, stating, "all of these developments occurred after the effective filing date of Wright's application and are of no significance regarding what one skilled in the art believed as of that date." Regarding the NOD mouse model comprising the "gold standard animal model", Applicant is reminded that distinguished immunologists such as Gerald Nepom and Matthias von Herrath have referred to the NOD model as a "workhorse" with numerous limitations, see von Herrath and Nepom (2009, of record). They note that just one of several NOD mouse strains even develops diabetes. They further note the ease of treating diabetes in the single NOD strain susceptible to diabetes, i.e., "over 200 perturbations of the immune environment are known that can prevent or reverse disease in NOD mice," treatments that have proven to be ineffective in humans (see Box 1). They conclude that the single strain of NOD mouse is susceptible to diabetes because of, "a rather unique set of genotypic circumstances that is unlikely to exist in a substantial fraction of the human population, if it exists at all" (page 130, column 1).

Applicant argues that treatment in humans is not required.

Applicant's position is noted. It must also be noted, however, that failures of treatments in humans cannot simply be ignored.

5. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

6. Claims 1-5, 7, 13, 15-19, and 22-24, and 26-30 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claims 1-7 and 13-16 of U.S. Patent Application No. 11/290,070. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the '070 application recite a method comprising treating IDDM with a GAD construct such as would be encompassed by that recited in Claim 1.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

7. Claims 1-5, 7, 13, 15-19, and 22-24, and 26-30 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claims 1-7 and 13-16 of U.S. Patent Application No. 11/425,084. Although the

conflicting claims are not identical, they are not patentably distinct from each other because the claims of the '084 application recite a method comprising treating IDDM with a GAD construct such as would be encompassed by that recited in Claim 1.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicant defers a response regarding the remaining double patenting rejections until the finding of allowable claims.

8. Claims 1-5, 7, 13, 15-19, and 22-24, and 26-30 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter written description rejection.

As set forth previously, The specification and the claims as originally filed do not provide support for the invention as now claimed, specifically:

A) A method comprising the administration of an immunoglobulin construct comprising a protein [fragment] (added 11/12/10) represented by SEQ ID NO:4 (Claims 1 and 13).

Applicant cites pages 13, 21, 45, and 26 in support of the claimed method.

A review of the specification reveals that the peptide of SEQ ID NO:4 is found at page 46 of the specification. The specification, however, does not teach the peptides as part of an immunoglobulin construct.

Applicant's arguments, filed 5/20/11, have been fully considered but are not found persuasive. Applicant now cites pages 4, 8, 19, 22-24, 45, and 46 of the specification.

A review of the cites shows that just the cite at pages 45-46 discloses the peptide of SEQ ID NO:4. The generic disclosures of "GAD2" at pages 4, 8, 19, and 22-24 cannot support the claimed method employing a specific chimeric construct, said construct comprising the specific amino acid sequence of SEQ ID NO:4 (TYEIAPVFVLLEYVT).

A review of pages 45 and 46, at the beginning of the Examples section, show that the peptide of SEQ ID NO:4 is disclosed just once, and only in the context of a peptide. It is not disclosed in the context of the claimed method of administering an Ig-GAD65 peptide construct for the delaying or preventing of type 1 diabetes. Indeed, the disclosure of the Examples is limited to the production and administration of a single Ig-insulin peptide (Ig-INSβ) and an Ig-hen egg lysozyme (Ig-HEL) control peptide. Even assuming that the cite supports an Ig-GAD65 construct employing the peptide of SEQ ID NO:4, it does not teach said construct comprising a CDR1, CDR2, and CDR3 as is claimed.

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claims 1, 2, 4, 5, 7, 13, 15-19, 22-24, 26, and 28-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 98/30706 in view of Chao et al. (1999).

As set forth previously, WO 98/30706 teaches the treatment of autoimmune disorders, including IDDM, (see particularly pages 10 and 19) employing an engineered fusion protein, e.g., a humanized IgG_{2b} chimeric protein wherein an autoantigen peptide is inserted into the D segment of a CDR3 loop (see particularly Figure 1, page 13, and Example II).

The method differs from the claimed invention only in that it does not teach the use of the GAD65 SEQ ID NO:4 peptide as the autoantigen employed for the treatment of IDDM.

Chao et al. teach that the GAD65 peptide of SEQ ID NO:4 (p206-220) is an immunodominant T cell diabetes antigen in their NOD mouse diabetes model (see particularly page 9300, Results).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to perform the method of WO 98/30706 for the treatment of IDDM in a subject such as a mouse model of diabetes employing the p206-220 T cell autoantigen of Chao et al. One of ordinary skill in the art at the time the invention was made would have had reason to select the GAD65 p206-220 peptide as the autoantigen of choice for use in the claimed method because Chao et al. teaches that it was the most immunodominant diabetes T cell antigen in their model. Regarding the timing of administration of the Ig-fusion protein set

forth in claims such as 3, 16, 17, etc., said timing would comprise only routine optimization which would fall well within the purview of one of skill in the art at the time of the invention.

Applicant's arguments, filed 5/20/11, have been fully considered but are not found persuasive. Applicant again argues that an obviousness rejection that relies on an alleged teaching, suggestion or motivation *must* be articulated in a *Graham v. Deere* format.

Again, Applicant is simply in error, the *Graham v. Deere* format is just one of many that may be used in a finding of obviousness. It is the substance of a rejection, not the format that is critical.

Applicant again argues a lack of expectation of success.

Applicant's argument seems puzzling given the fact that as of the effective filing date of the instant application the record contains no evidence that Applicant had performed the method of the instant claims, even in their limited animal model. And it is unclear how Applicant can convincingly ignore the Inventor's own teaching (in WO 98/30706) that the Ig chimeric construct can be employed in the treatment of various T cell mediated disorders, including insulin dependent (type 1) diabetes, by simply changing the antigen (pages 10 and 19).

Applicant argues unexpected results.

Applicant is advised that a persuasive claim of unexpected results first requires that the unexpected results be commensurate in scope with the invention as claimed. Such is clearly not the case here. Second, evidence of unexpected results generally takes the form of a direct comparison of the claimed invention with the closest prior art which is commensurate in scope with the claims. In this instance it is noted that no comparison with any other treatment has been performed. Accordingly, Applicant's allegations of unexpected results is not persuasive.

Applicant argues that the prior art does not teach the step of administering the claimed therapy after autoantibody seroconversion.

After autoantibody seroconversion would be the most obvious time to administer treatment of the instant claims. The ordinarily skilled artisan would have viewed this timeframe as the time at which the onset of actual disease could be delayed or prevented in a subject now proven likely to develop disease (because of the seroconversion).

11. No claim is allowed.

12. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Gerald Ewoldt whose telephone number is (571) 272-0843. The examiner can normally be reached Monday through Thursday from 7:30 am to 5:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ram Shukla, can be reached on (571) 272-0735.

14. **Please Note:** Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197

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